

REMARKS

Claims 1-19 are pending in this application and were subject to a restriction requirement. Claims 12-16 are withdrawn from consideration by election filed on July 21, 2004. Claims 1-11 and 17-19 stand rejected. Claims 1 and 4 are amended herein. No claim is objected to.

35 U.S.C. § 112, second paragraph

Claims 1-11 and 17-19 stand rejected under 35 U.S.C. § 112, second paragraph for allegedly being indefinite for failing to particularly point out and distinctly claim the subject matter which Applicant regards as the invention. Specifically, the Examiner alleges that claims 1 and 19 recite the language, "incubation times," which renders the claims vague and indefinite because the term is a relative term. Applicant respectfully submits that the term "incubation time" is described throughout the specification. Particularly, Applicant points to Figures 1, 2 and 4 and the descriptions of Figures 1, 2, and 4 in the application where, "incubation time" is described as a range of several timepoints that occur over a given time course. Such a range of times is understood by the skilled artisan to be relative to each other from a selected starting point.

The Examiner also alleges that claim 2 recites the term "biomolecule" which renders the claim indefinite, because it is "unclear what molecular structures are or are not encompassed by the term." Applicant respectfully submits that the term "biomolecule" is known throughout the art and can be found in several ordinary dictionaries. In fact, the Examiner characterizes "protein enzymes, peptides, nucleic acids, etc." as examples of biomolecules in his discussion of Moore, *et al.*

Claim 4 stands rejected because it misspells the word "dimensional" and allegedly recites and improper Markush group. Applicant amends claim 4 herein to correct these two typographical errors. In addition, Applicant amends claim 1 herein to correct typographical errors.

Claim 18 also stands rejected, because the Examiner alleges that the language "at a selected time" is vague and indefinite. The Examiner alleges that "it seems to read on a mental step and it is unclear as to who selected the time or what is selected." Applicant respectfully submits that as discussed above incubation times are described throughout the application. Similarly, a "time" to quench an incubation is described at, for instance, page 7, lines 1-9 and page 14 line 1 through page 15, line 2. It will be understood by the skilled artisan that incubation times may occur over a time range from which certain timepoints may be "selected" by the skilled artisan.

Applicant respectfully submits that in view of the forgoing remarks and the claims as amended, Applicant have overcome the Examiner's rejection under 35 U.S.C. §112, second paragraph and that this rejection should be withdrawn.

35 U.S.C. § 102

Claims 1-4, 6, 7, 9-11, 17, 18, and 19 stand rejected under 35 U.S.C. 102(e) as being anticipated by Moore, *et al.* U.S. 2003/0143757 (hereinafter “Moore, *et al.*”). Specifically, the Examiner alleges that Moore, *et al.* teach obtaining an NMR of a ligand, exposing the ligand to the target and generating a subsequent NMR spectrum of the ligand. The Examiner also alleges that Moore, *et al.* also, “contemplates targets that are protein, enzymes peptides, nucleic acids, etc., which are biomolucules.” Applicant respectfully submits that a single prior art reference anticipates a claimed invention only if it identically shows every element of the claimed invention. *In re Bond*, 15 U.S.P.Q.2d 1566 (Fed. Cir. 1990). With respect to independent claims 1 and 19 of the instant application, substrate (product or ligand) and chemical compounds and target molecules are exposed to each other for “one or more incubation times.” Moore, *et al.* do not contemplate exposing substrate, ligand or product of a target molecule with chemical compounds and generating a spectrum of that mixture. Furthermore, Moore, *et al.* do not disclose exposing this mixture with a target molecule for one or more incubation times and comparing NMR spectra of the target/compound/ligand mixture over time. Finally, Moore, *et al.* do not monitor a signal generate by a substrate, ligand or product over time. Instead, they observe the signal of a chemical compound in a single mixture. Thus, Moore, *et al.* do not identically show each and every element of the independent claims of this invention.

In addition, claims 1-11, 18 and 19 stand rejected under 35 U.S.C. 102(b) as being anticipated by Thompson *et al.*, *Proc. Natl. Acad. USA*, Vol. 94 pp. 14249-14254 (Dec. 1997). The Examiner alleges that Thompson, *et al.* teach “proton NMR characteristics of inhibitors of cysteine protease, a biomolecule, wherein the inhibitors were synthesized with isotope ³H, followed by NMR analysis of cathepsin K adducts.” The Examiner further alleges that the abstract and figure 4 of this paper indicate that the protease and inhibitors are “incubated with 2-(N-morpholino)ethane-sulfonic acid (Mes/NaCl/Cts) for fixed times depending on inhibitor concentration whereupon reactions are quenched by dialysis.” Applicant respectfully submits that Thompson, *et al.* do not disclose mixing substrate, product or ligand and chemical compounds to generate a first spectrum, nor do they disclose exposing a mixture of substrate and chemical compound with a target molecule and comparing spectra from this mixture over one or more incubation times. Thompson, *et al.*, merely disclose a selectively double-labeled inhibitor alone or with cathepsin K followed by a ¹⁵N-decoupled spectrum of the same mixture (see figure 4 a-c in Thompson, *et al.*). Applicant also respectfully submits that paragraph 3, page 14250 of Thompson, *et al.* merely discloses sample preparation for multiple incubation times for MS analysis. The same paragraph clearly indicates that a *single* sample was prepared for NMR analysis as shown in figure 4 (*emphasis added*).

Claims 1-11, 18 and 19 stand rejected under 35 U.S.C. 102(b) as allegedly being anticipated by Hajduk, *et al.* *J. Am. Chem. Soc.* 1997 Vol. 119 pp. 12257-12261. Specifically, the

Examiner alleges that Hajduk, *et al.*, “teach identifying compounds that bind to macromolecules by one-dimensional NMR, which exploits changes in either the relaxation rates or diffusion rates of a small compound.” Applicant respectfully submits that Hajduk, *et al.* merely disclose using one-dimensional relaxation- and diffusion-edited strategies to detect compound binding affinity to a target molecule. In other words, compound peaks were removed from the spectrum of compound and target by altering allowed relaxation time by changing the spin-lock times, using CPMG signaling, or by changing pulse field gradient strength, respectively. Hajduk, *et al.* do not teach mixing substrate, product or ligand and chemical compounds to generate a first spectrum, nor do they teach exposing a mixture of substrate and chemical compound with a target molecule and comparing spectra from this mixture over one or more incubation times. Thus, Hajduk, *et al.* do not teach each and every element of the instantly claimed invention.

Claims 1-4, 6, 7, 9-11, 17 and 19 also stand rejected under 35 U.S.C. § 102(b) as allegedly being anticipated by Fesik, *et al.* (WO 98/48264 hereinafter “Fesik, *et al.* I”). Specifically, the Examiner alleges that Fesik, *et al.* I teach generating diffusion-filtered proton spectrum of “one or a mixture of compounds,” exposing one or a mixture of compounds to a target and comparing the first and second spectra. Applicant respectfully submits that Fesik, *et al.* I describe T2-filtered or relaxation-edited NMR screening techniques or diffusion-edited screening techniques, similar to those presented in Hajduk, *et al.* Fesik, *et al.* I merely disclose a comparison of a spectrum of ligand alone with a spectrum of ligand mixed with target molecule, wherein the presence of target molecule significant effects T2 relaxation time of residual peaks on the ligand. Thus, Fesik, *et al.* I relies on the increased tumbling time of a ligand when combined with a target molecule. Similarly, Fesik, *et al.* I also relies on increased diffusion rate of a small molecule when combined with a large target molecule, by using weak and strong gradient strength on ligand combined with target molecule and obtaining difference spectra. Fesik, *et al.* I do not disclose mixing substrate, product or ligand and chemical compounds to generate a first spectrum, nor do they teach exposing a mixture of substrate and chemical compound with a target molecule and comparing spectra from this mixture over one or more incubation times. They examine only spectra of chemical compounds at a single timepoint and not of substrate, ligand or product with chemical compound and target molecule over time. Thus, Fesik, *et al.* I do not teach each and every element of the instantly claimed invention.

Claims 1-4, 6, 7, 9-11, 17 and 19 also stand rejected under 35 U.S.C. § 102(b) as allegedly being anticipated by Fesik, *et al.* (WO 97/18469 hereinafter “Fesik, *et al.* II”). The Examiner alleges that Fesik, *et al.* II teach screening chemical compounds for binding a given target molecule using 15N/1H NMR correlation spectrum. Applicant respectfully submits that Fesik, *et al.* II teach similar techniques to Fesik, *et al.* I with the exception that the NMR spectra to be compared is two-dimensional. For instance, Example 2 of Fesik, *et al.* II discloses 15N/1H NMR comparing

stremolysin with and without test compounds and comparing the resulting spectrum. More importantly, Fesik, *et al.* II discloses spectra of the target molecule and not of a substrate. Fesik, *et al.* II also do not disclose mixing substrate, product or ligand and chemical compounds to generate a first spectrum, nor do they teach exposing a mixture of substrate and chemical compound with a target molecule and comparing spectra from this mixture over one or more incubation times. Thus, Fesik, *et al.* II do not teach each and every element of the instantly claimed invention.

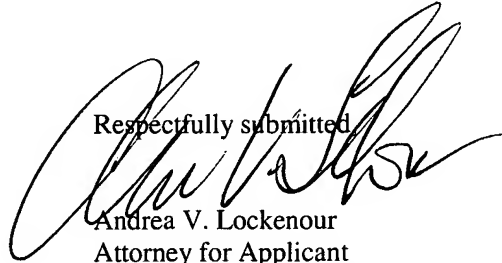
Claims 1, 2, 3, 10, 11, and 19 also stand rejected under 35 U.S.C. § 102(b) as allegedly being anticipated by Deem, *et al.* (WO 96/30849). The Examiner alleges that Deem, *et al.* teach NMR measurements of molecules that bind to targets, wherein the targets include proteins, “and wherein comparing spectra comprises an algorithm or a computer algorithm.” Applicant respectfully submits that Deem, *et al.* does not disclose comparing spectra of ligand and chemical compound and target molecule at one or more incubation times. Deem, *et al.* merely suggests methods of predicting an active drug or pharmacophore by comparing distances of atoms from a library of active compounds.

Claim 19 also stands rejected under 35 U.S.C. § 102(b) as allegedly being anticipated by Wither, *et al.* (U.S. 5,716,812). Specifically, the Examiner alleges that Wither, *et al.* teach ¹H-NMR analysis of products of enzymatic transglycosylation reaction. Applicant respectfully submits that Wither, *et al.* merely suggest using ¹H-NMR techniques to determine the structure of catalytic intermediates from an enzymatic reaction. Wither, *et al.* do not disclose mixing substrate, product or ligand and chemical compounds to generate a first spectrum, nor do they teach exposing a mixture of substrate and chemical compound with a target molecule and comparing spectra from this mixture over one or more incubation times. Thus, Wither, *et al.* do not teach each and every element of the instantly claimed invention.

Applicant respectfully submits that in view of the forgoing remarks, Applicant has overcome the Examiner's rejection under 35 U.S.C. §102(b) for independent claims 1 and 19 and that these rejections should be withdrawn. As claims 2-11, 17 and 18 depend from claim 1, either directly or indirectly, Applicant believes rejection of these claims should also be withdrawn.

Applicant reserves the right to prosecute, in one or more patent applications, the claims to non-elected inventions, the cancelled claims, the claims as originally filed, and any other claims supported by the specification. Applicant thanks the Examiner for the Office Action and believes this response to be a full and complete response to such Office Action. Accordingly, favorable reconsideration and allowance of the pending claims is earnestly solicited. If it would expedite the prosecution of this application, the Examiner is invited to confer with the Applicant's undersigned attorney.

Respectfully submitted,



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